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(54) Title: NASAL DELIVERY OF SILDENAFIL CITRATE

(57) Abstract

Intranasal dosage units of cyclic guanosine monophosphate–specific phosphodiesterase inhibitors are described which are combined with suitable intranasal carriers having a buffer, surfactants and absorption enhancers. The pH of the buffer and concentration of the surfactant are selected to facilitate absorption of the inhibitor across the nasal mucosa of a mammal in order to achieve a peak plasma concentration of the inhibitor in less than 1 hour, and desirably within 30 minutes of administration.

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NASAL DELIVERY OF SILDENAFIL CITRATE

This application claims the benefit of U.S. Provisional Application No. 60/090,941, filed June 26, 1998, the entire disclosure is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates generally to the intranasal delivery of cyclic guanosine monophosphate-specific phosphodiesterase inhibitors to a mammal. More particularly, pharmaceutical compositions for the treatment of various diseases, including impotence, are disclosed which compositions are dispersed in nasal delivery vehicles. Methods of treatment via various nasal delivery systems are also provided.

BACKGROUND OF THE INVENTION

The use of cyclic guanosine 3′,5′-monophosphate phosphodiesterase (cGMP PDE) inhibitors to treat a variety of cardiovascular disorders including angina, hypertension, heart failure and atherosclerosis is well known. For example, U.S. Patent Nos. 5,250,534, 5,272,147 and 5,426,107 assigned to Pfizer Inc. which are hereby incorporated by reference reportedly describe a series of pyrazolo[4,3-d]-pyrimidin-7-ones which are potent and selective inhibitors of cGMP PDE. Recently, International Publication No. WO 94/28902 to Pfizer Limited, which is hereby incorporated by reference, reportedly described the use of pyrazolopyrimidiinones for the treatment of impotence.

It is believed that certain medical conditions result in elevated levels of cGMP PDE in a mammal. These elevated levels of cGMP PDE can lead to sexual dysfunction, including impotence. Accordingly, administration of cGMP PDE inhibitors block the action of endogenous cGMP PDE and allows for the relaxation of the corpus cavernosum tissue of a penis which in turn allows blood to flow into the penis and subsequent erection.

These compositions are reported to have therapeutic activity when administered orally, intravenously, buccally or sublingually. These traditional methods of delivery, however, suffer from a variety of draw backs. For example, drugs administered orally suffer from the well know "first pass effect" in which the environment of the stomach denatures and/or degrades large amounts of the drug before a therapeutically effective amount is absorbed. Intravenous delivery of such drugs is painful and is not tolerated well by certain patients. Buccal and sublingual delivery of such drugs is often slow and can lead to degradation of the drug by enzymes in the oral cavity. Furthermore, each of these traditional delivery mechanisms take an hour or longer before peak plasma concentration of the inhibitor is reached. The relatively long lag time between administration of such inhibitors and their physiologic effect is thus not optimal because of the time it takes to achieve peak plasma concentrations. Thus, in human sexual encounters, one hour lag between administration of the inhibitor and its desired effect is inconvenient.

Thus, there is a need for a delivery system for such cGMP PDEs that ensures delivery of therapeutic amounts of the drug into the blood stream which is both fast acting and easily administered. The present invention is directed to meeting these and other needs.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for the treatment of sexual dysfunction in a mammal. This composition includes a cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor in combination with a nasal delivery vehicle. In another embodiment of the present invention, a method is provided for treating impotence in humans that includes nasally administering the above-referenced composition.

Another embodiment is a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor dispersed in a buffer to maintain the pH of the inhibitor, a pharmaceutically acceptable thickening agent, a humectant and a pharmaceutically acceptable surfactant. In another embodiment, a method of treating impotence, angina, hypertension, pulmonary hypertension, heart failure, atherosclerosis and glaucoma in a human in need of such treatment includes administering to a nasal membrane of the human an effective amount of this pharmaceutical composition.

In a further embodiment, there is provided a method of treating impotence in a mammal. This method includes administering into a nasal cavity of the mammal a therapeutically effective dosage of a cyclic guanosine monophosphate specific phosphodiesterase inhibitor in combination with a nasal delivery vehicle that includes a pharmaceutically acceptable buffer, thickening agent, humectant and surfactant.

In another embodiment, there is provided a method of administering a therapeutically effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor to a mammal through a nasal membrane. This method includes delivering to a nasal membrane of the mammal the inhibitor dispersed in a nasal delivery vehicle that includes a pharmaceutically acceptable buffer, thickening agent, humectant and surfactant.

In another embodiment, an intranasal dosage unit is provided for treating impotency in a mammal. This dosage unit includes an effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor in combination with an intranasal delivery formulation. This delivery formulation includes a buffer and an effective amount of a surfactant. The pH of the buffer and the concentration of the surfactant are selected to facilitate the absorption of the inhibitor so that a peak plasma concentration of the inhibitor is achieved in less than one hour, desirably in less than

45 minutes, such as for example, in about 10 to about 20 minutes of administering the dosage unit to a nasal mucosa of the mammal.

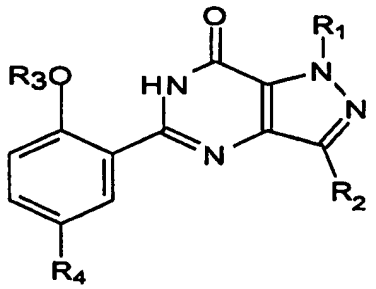
The present invention will be more fully understood by a reading of the section entitled "Detailed Description of the Invention".

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to pharmaceutical compositions and methods for treating sexual dysfunction in a mammal which composition includes a cyclic guanosine monophosphate-specific inhibitor in combination with a nasal delivery vehicle.

For purposes of the present invention, the phrase "sexual dysfunction" is intended to encompass medically related symptoms resulting in the inability of a male or female to perform sexually, including male impotence. As used herein, the term "impotence" is intended to mean the inability of a male to achieve and/or sustain a penile erection sufficient for vaginal penetration and intercourse.

The cyclic guanosine monophosphate-specific phosphodiesterase inhibitors of the present invention are well known in the art and are set forth in U.S. Patent Nos. 5,250,534, 5,272,147, 5,426,107 and International Publication No. WO 94/28902. In particular, these cGMP PDE inhibitors include compounds of the formula (I):



wherein R_1 is H; C_1-C_3 alkyl; C_3-C_5 perfluoroalkyl; or C_3-C_5 cycloalkyl; R_2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl or C_3-C_6 cycloalkyl; R_3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl; R_4 is C_1-C_4 alkyl optionally substituted with OH, NR_5R_6, CN, $CONR_5R_6$ or CO_2R_7; C_2-C_4 alkenyl optionally substituted with CN, $CONR_5R_6$ or CO_2R_7; C_2-C_4 alkanoyl optionally substituted with NR_5R_6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR_5R_6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR_5R_6; $CONR_5R_6$; CO_2R_7; halo; NR_5R_6; $NHSO_2NR_5R_6$; $NHSO_2R_8$; $SO_2NR_9R_{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl; R_5 and R_6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R_{11})-piperazinyl or imidazolyl group wherein this group is optionally substituted with methyl or OH; R_7 is H or C_1-C_4 alkyl; R_8 is C_1-C_3 alkyl optionally substituted with NR_5R_6; R_9 and R_{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R_{12})-piperazinyl group wherein this group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR_{13}R_{14}$ or $CONR_{13}R_{14}$; R_{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl; R_{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R_{13}R_{14}$N)C_2-C_6 alkyl; ($R_{13}R_{14}$NOC)C_1-C_6 alkyl; $CONR_{13}R_{14}$; $CSNR_{13}R_{14}$; or C(NH)$NR_{13}R_{14}$; and R_{13} and R_{14} are each independently H; C_1-C_4alkyl; (C_1-C_3 alkoxy)C_2-C_4; or (hydroxy)C_2-C_4 alkyl; or a chemically modified equivalent thereof or a pharmaceutically acceptable salt thereof.

Furthermore, the present compositions also include all classes of PDE inhibitors including the type II, III and V inhibitors identified in International Publication No. WO 94/28902, as well as all pyrazolopyrimidinones which are effective for treating sexual dysfunction in a mammal, including impotence.

Desirably, the composition set forth in formula I above is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-

ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate, also known as Sildenafil Citrate sold under the trademark Viagra™ by Pfizer Inc. Moreover, the cGMP PDE inhibitors of the present invention can also include chemically modified equivalents of Sildenafil Citrate. As used herein, "chemically modified equivalents" includes pharmaceutical salts, derivatives, analogs, homologs, free bases and other chemical variations of the compositions set forth above which do not significantly alter the structure or function thereof.

It has been unexpectedly found that by combining the cGMP PDE inhibitor compositions disclosed above in a nasal delivery vehicle that peak plasma concentration of these compositions is achieved within about 30 minutes or less as compared to 1 hour or longer for non-nasal delivery routes. The nasal delivery vehicles that can be used with the present invention can take various forms including for example, powders, powder microspheres, solutions, gels, nano-particle suspensions, suspensions, liposomes, emulsions and microemulsions.

As used herein, nano-particle suspensions are made by milling powders of the present pharmaceutical compositions to a micronized size. Delivery vehicles made from such nano-particles provide superior absorbability for compositions having generally poor solubility.

The various forms of the delivery vehicle set forth above can include a buffer to maintain the pH of the inhibitor, a pharmaceutically acceptable thickening agent, humectant and surfactant. Desirably, the pH of the buffer is selected to maintain the inhibitor in an un-ionized form. In particular, the pH of the buffer is selected to optimize the absorption of the inhibitor across the nasal mucosa. The particular pH of the buffer, of course, can vary depending upon the particular nasal delivery formulation, as well as the specific inhibitor composition selected. Buffers that are suitable for use in the present invention include, for example, acetate, citrate and phosphate buffers.

In the present invention, the pH of the compositions should be maintained from about 3 to about 10. Compositions having a pH of less than about 3 or greater than about 10 can increase the risk of irritating the nasal mucosa of a recipient.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include for example, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer and mixtures thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents will also be used in the particulate formulations of the present invention.

The compositions of the present invention also include a humectant or a soothing/moisturizing agent to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used in the present invention include, for example, sorbitol, propylene glycol and glycerol. The concentration of the humectant or soothing/moisturizing agent(s) in the present compositions will also vary with the agent selected.

In order to enhance absorption of the cGMP PDE inhibitors through the nasal mucosa, a therapeutically acceptable surfactant is added to the nasal delivery vehicle. Suitable surfactants that can be used in accordance with the present invention include, for example, polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides, such as for example, Tween 80, Polyoxyl 40 Stearate, Polyoxy ethylene 50 Stearate, fusieates, bile salts and Octoxynol. Suitable surfactants include non-ionic, anionic and cationic surfactants. These surfactants can be present in the delivery vehicle in a concentration ranging from about 0.001% to about 20% by weight. Particulate formulations may also contain suitable surfactants.

In the present invention other optional ingredients may also be incorporated into the nasal delivery vehicle provided they do not interfere with the action of the

inhibitor or significantly decrease the absorption of the inhibitor across the nasal mucosa. Such ingredients can include, for example, pharmaceutically acceptable excipients and preservatives. The excipients that can be used in accordance with the present invention include, for example, bio-adhesives and/or swelling/thickening agents.

In the present invention, any other suitable absorption enhancers as known in the art may also be used in both the non-particulate and particulate formulations set forth herein.

To extend shelf life, preservatives can be added to the present compositions. Suitable preservatives that can be used with the present compositions include, for example, benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium, with benzalkonium chloride being preferred. Typically, the preservative will be present in the present compositions in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

In another embodiment of the present invention, the compositions as described above are administered nasally to a mammal to treat impotence. For purposes of the present invention, "administered nasally" or "nasal administration" is intended to mean that the cGMP PDEs are combined with a suitable delivery vehicle for absorption across the nasal mucosa of a mammal, desirably a human.

Another embodiment of the present invention is a nasally administered pharmaceutical composition that includes a therapeutically effective amount of a cyclic monophosphate-specific phosphodiesterase inhibitor dispersed in a buffer to maintain the pH of the inhibitor, a pharmaceutically acceptable thickening agent, a humectant and a pharmaceutically acceptable surfactant. As used herein, "therapeutically effective amount" means a unit dosage of the present inhibitors which is able to be combined with a pharmaceutically acceptable nasal delivery vehicle and

absorbed through the nasal mucosa of a mammal to provide a peak plasma concentration within the mammal of the inhibitor in less than 1 hour, desirably in less than about 45 minutes, such as for example, from about 20 to about 30 minutes, and which renders the intended physiological effect, such as for example to allow an erection in an impotent mammal.

Desirably, the cGMP PDE inhibitor is a cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor. More desirably, the inhibitor is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

The present nasally administered pharmaceutical compositions can be used to treat a wide variety of disorders including for example, stable, unstable and variant angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, such as for example, post-percutaneous transluminal coronary angioplasty, peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility, e.g., irritable bowel syndrome, as well as sexual dysfunction, including for example impotence.

More particularly, in a further embodiment of the present invention, a method of treating impotence is provided. This method includes administering into a nasal cavity of a mammal for absorption through the nasal mucosa thereof a therapeutically effective dosage of a cGMP PDE inhibitor as previously set forth in combination with a nasal delivery vehicle. The inhibitor is a cGMP PDE inhibitor and includes sildenafil citrate and chemically modified equivalents thereof. For purposes of the present invention, the nasal delivery vehicle can include, for example, a pharmaceutically acceptable buffer, a thickening agent a humectant and a surfactant.

In a further embodiment of the present invention, a method is provided for administering a therapeutically effective amount of a cGMP PDE inhibitor to a

mammal through a nasal membrane. This method includes delivering to a nasal membrane of a mammal the inhibitor dispersed in a nasal delivery vehicle that includes a pharmaceutically acceptable buffer, thickening agent, humectant and surfactant. In this method, the cGMP PDE inhibitor is effective for the treatment of a sexual dysfunction in a mammal, particularly impotence in man. The method is also suitable for treating for example, angina, hypertension, pulmonary hypertension, heart failure, atherosclerosis and glaucoma.

A further embodiment of the present invention is provided that includes an intranasal dosage unit for treating impotency in a mammal. This intranasal dosage unit includes an effective amount of a cGMP PDE inhibitor in combination with a pharmaceutically acceptable intranasal carrier. This carrier includes a buffer and an effective amount of a surfactant. The pH of the buffer and the concentration of the surfactant are selected as set forth above to facilitate cGMP PDE inhibitor absorption through the nasal mucosa so that peak plasma concentrations of the inhibitor is achieved in less than 45 minutes, desirably in less than 30 minutes, and most desirably in less than 20 minutes after administration.

The pharmaceutically acceptable carrier of the present invention will vary depending upon the exact nature of the particular dosage form required. Suitable dosage forms that can be used with the present cGMP PDE inhibitors are found in Remington's Pharmaceutical Sciences, 18th. ed. (1995) which is hereby incorporated by reference, and include for example, nano-particle suspensions, suspensions, ointments, gels, solutions, simple powders, powder microspheres, liposomes, emulsions or microemulsions.

The powder microspheres according to the present invention can be formed from, for example, various polysaccharides and celluloses including starch, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, alginate and chitosan.

The intranasal dosage form of the present invention can include an absorption enhancer and/or an excipient as previously described.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating sexual dysfunction in a mammal comprising a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor in combination with a nasal delivery vehicle.

2. The pharmaceutical composition of claim 1 wherein said inhibitor is selected from the group consisting of type II, type III and type V PDE inhibitors.

3. The pharmaceutical composition of claim 1, wherein said cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

4. The pharmaceutical composition of claim 3, wherein said nasal delivery vehicle comprises a buffer to maintain the pH of said inhibitor, a pharmaceutically acceptable thickening agent, a humectant and a pharmaceutically acceptable surfactant.

5. The pharmaceutical composition of claim 4 further comprising one or more pharmaceutical excipients.

6. The pharmaceutical composition of claim 5 further comprising a pharmaceutically acceptable preservative.

7. The pharmaceutical composition of claim 4, wherein said buffer is selected from the group consisting of acetate, citrate and phosphate buffers.

8. The pharmaceutical composition of claim 4, wherein said thickening agent is selected from the group consisting of methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer and mixtures thereof.

9. The pharmaceutical composition of claim 4, wherein said humectant is selected from the group consisting of sorbitol, propylene glycol, glycerol and mixtures thereof.

10. The pharmaceutical composition of claim 4, wherein said surfactant is selected from the group consisting of polyoxyethylene derivatives and fatty acid partial esters of sorbitol anhydrides.

11. The pharmaceutical composition of claim 4, wherein said surfactant is selected from the group consisting of sodium lauryl sulfate, Tween 80, Polyoxyl 40 Stearate, Polyoxy ethylene 50 Stearate, fusieates, bile salts and Octoxynol.

12. The pharmaceutical composition of claim 4, wherein said surfactant is selected from the group of anionic, cationic and nonionic surfactants.

13. A method of treating impotence in a male mammal comprising nasally administering the composition according to claim 1.

14. The pharmaceutical composition of claim 1, wherein said inhibitor is selected from the group consisting of sildenafil citrate, chemically modified equivalents and pharmaceutical salts thereof.

15. A nasally administered pharmaceutical composition comprising a therapeutically effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor dispersed in a buffer to maintain the pH of said inhibitor, a pharmaceutically acceptable thickening agent, a humectant and a pharmaceutically acceptable surfactant.

16. The nasally administered pharmaceutical composition of claim 15, wherein said cyclic guanosine monophosphate-specific phosphodiesterase type V inhibitor is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1-H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

17. A method of treating impotence, angina, hypertension, pulmonary hypertension, heart failure, atherosclerosis and glaucoma in a human in need of such treatment comprising administering to a nasal membrane of said human an effective amount of a composition according to claim 15.

18. A method of treating impotence in a mammal comprising administering into a nasal cavity of said mammal a therapeutically effective dosage of a cyclic guanosine monophosphate specific phosphodiesterase inhibitor in combination with a nasal delivery vehicle comprising a pharmaceutically acceptable buffer, thickening agent, humectant and surfactant.

19. The method of claim 18, wherein said inhibitor is selected from the group consisting of sildenafil citrate, chemically modified equivalents and pharmaceutical salts thereof.

20. A method of administering a therapeutically effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor to a mammal through a nasal membrane comprising delivering to said nasal membrane said inhibitor dispersed in a nasal delivery vehicle comprising a pharmaceutically acceptable buffer, thickening agent, humectant and surfactant.

21. The method of claim 20, wherein said inhibitor is effective for the treatment of sexual dysfunction in a mammal.

22. The method of claim 20, wherein said inhibitor is effective for the treatment of angina, hypertension, pulmonary hypertension, heart failure, atherosclerosis and glaucoma.

23. An intranasal dosage unit for treating impotency in a mammal comprising an effective amount of a cyclic guanosine monophosphate-specific phosphodiesterase inhibitor in combination with an intranasal carrier comprising a buffer and an effective amount of a surfactant, wherein buffer pH and surfactant concentration are selected to enhance absorption of said inhibitor and to produce a peak plasma concentration of said inhibitor within 45 minutes of administering said dosage unit to a nasal mucosa of said mammal.

24. The intranasal dosage unit of claim 23, wherein said intranasal carrier is selected from the group consisting of simple powders, powder microspheres, solutions, gels, suspensions, nano-particle suspensions, liposomes, emulsions and microemulsions.

25. The intranasal dosage unit of claim 24 further comprising an absorption enhancer.

26. The intranasal dosage unit of claim 24 further comprising an excipient having bio-adhesive properties.

27. The intranasal dosage unit of claim 24 wherein said microspheres are formed from the group consisting of starch, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, alginate and chitosan.

28. The intranasal dosage unit of claim 23, wherein said buffer pH and said surfactant concentration are selected to enhance absorption of said inhibitor and to produce a peak plasma concentration of said inhibitor within 30 minutes of administering said dosage unit to a nasal mucosa of said mammal.

29. The intranasal dosage unit of claim 23, wherein said buffer pH and said surfactant concentration are selected to enhance absorption of said inhibitor and to produce a peak plasma concentration of said inhibitor within 20 minutes of administering said dosage unit to a nasal mucosa of said mammal.

30. The intranasal dosage unit of claim 23, wherein said buffer is selected to have a pH of from about 3 to about 10.

31. The intranasal dosage unit of claim 23, wherein said surfactant concentration is from about 0.001% to about 20% by weight.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14352

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/495, 31/50
US CL :514/253
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/253

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, USPATFULL, HCAPLUS- sildenafil in intranasal preparations for the treatment of impotence. Intranasal preparations useful in the treatment of impotence.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MURRAY, K.J. Phosphodiesterase VA Inhibitors. DN&P. April 1993, Vol. 6, No. 3, pages 150-156, especially pages 153-55.	1-31
Y	Database HCAPLUS on STN, American Chemical Society, AN 1995:412879, WO 9428902 A1 (ELLIS et al.), abstract.	1-31
Y	Database MEDLINE on STN, US National Library of Medicine, (Bethesda, MD, USA), AN 95159287, HEATON, J.P. et al. 'Recovery of erectile function by the oral administration of apomorphine,' abstract, Urology, Feb 1995.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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